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October 27, 1999

Docket No. 99D-2335
Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

To Whom It May Concern:

We applaud the FDA's apparent overall goal to lower the protein content of natural rubber latex gloves and thereby reduce the symptom severity of latex allergic individuals and potentially reduce the rate of sensitization in high risk groups. However, we have several serious concerns detailed below regarding the proposed regulations.

1. **Protein Labeling (*Proposed 21 CFR 801.440*)**
   The FDA proposes to amend the existing latex cautionary label ("*Caution: This product contains natural rubber latex which may cause allergic reactions.*") by adding an additional statement as to latex protein content: "*The FDA recommends that this product contain no more than 1200 µg extractable protein per glove. This product contains _____ µg extractable protein per glove.*"

   First, the units used in this statement are not consistent with the recently revised 1999 ASTM rubber glove standards (ASTM D3577 and D3578) or the Malaysian Rubber Board Standards, which use mg per decimeter^2. Because the latter unit reflects surface area rather than weight, it better addresses the issue of surface protein level and does not apply a different standard to a large glove versus an extra-small glove. Either these units or the ASTM units should be modified to be consistent with one another.

   Based on our recent analysis of approximately 20 brands of powdered and powder-free latex gloves, most of the powder-free brands would comply with this labeling standard whereas a large portion of the powdered gloves would not. If this standard is not intended to apply to existing gloves (but only new 510*k* applicants), it will have little impact on the majority of gloves currently available in the United States and will, therefore, fail to accomplish the intended goal of lowering latex glove protein content for the benefit of end users.

   Furthermore, the mixing of protein content labeling and cautionary statements sends a badly mixed message to the end user and is particularly confusing for gloves with lower protein levels. We frequently hear from latex allergic consumers who believe it is safe for them to use a "low protein" or "hypoallergenic" glove. Despite the current regulations, there are still latex glove products using these marketing claims. These new changes further muddy the consumers' vision of the

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issues. Content labeling should not be mixed with caution statements. An analogy that illustrates the problems encountered by this confusing approach can be found in cigarette marketing claims. If "Caution: The Surgeon General has determined smoking can be hazardous to your health," was followed by "The FDA recommended the nicotine/carcinogen level be below___," the emphasis and credibility of the warning label would be severely undermined.

Finally, the additional or alternate caution statement proposed for those gloves with a protein content less than 50 µg per gram (or 300 µg per glove) should be applied to all latex gloves, not just to those below the "detection" limit for the inherently problematic Lowry assay. The safe use of any latex glove by NRL-sensitized individuals is simply an oxymoron. As noted in the medical literature, while Lowry protein levels generally correlate with symptom responses, Lowry total protein level is not an absolute predictor of antigenic protein content. Furthermore, there are no established total or antigenic protein concentration thresholds for symptom elicitation or sensitization.

In general, the Lowry assay is subject to significant variability (as noted in the 1999 ASTM standards) and should not be misinterpreted until these technical issues can be resolved. Our recent analysis of nearly 40 brands of latex gloves analyzed by the Lowry method in two different laboratories showed as much as a 20 µg/g difference between results for powder free latex brands (those most likely to bear a different label). In addition, antigenic (LEAP) protein content varied considerably on these same samples, and not all latex gloves with Lowry contents less than 50 µg per gram had similarly low LEAP values. As the FDA is no doubt aware, subtle changes in Lowry assay procedures between laboratories can influence extraction efficiency, artificially lower NRL protein content (Koch, 1997), and affect assay sensitivity (Yip, 1997). Chemicals commonly added during the manufacture of NRL can also interfere with the Lowry assay (Chen *et al.*, 1997). We have also observed LEAP and Lowry values about the detection limits on nitrile and vinyl gloves. Clearly, neither the current Lowry or LEAP assay methods are robust enough to discriminate reliably and dictate safety thresholds.

2. **Powder labeling (*Proposed 21 CFR 801.440*)**
We believe this proposed caution statement is inappropriately overstated and strong: *"Caution: Glove powder is associated with adverse reactions. FDA recommends that this product contain..."* It seems ludicrous that natural rubber latex (associated by the FDA with several fatalities and serious occupational health problem) and powder produces only *allergic* reactions, while glove powder on synthetic non-latex gloves produces *adverse* reactions. Why is a similar statement not included on natural rubber latex glove proposed labeling where the majority of health hazard documentation has been generated?

With regard to the 120 mg per glove limit proposed, we are concerned with the determination basis for this threshold. Historically, the use of powdered gloves during surgeries has been associated with an increased incidence of granulomas and peritoneal adhesions as summarized by the FDA Glove Powder Report in September 1998. However, while the studies are well documented, they often failed to distinguish the type of powder (cornstarch, talc, etc.) or glove material (NRL or other) used. Many factors are suspected to play a role in this problem, such as the method of sterilization, allergic reactions to cornstarch (or NRL, or other contaminants), endotoxins and

contamination with microorganisms. Recent published studies demonstrate that glove powder on latex gloves contributes significantly to symptom severity and IgE levels in latex allergic workers, and may facilitate sensitization of non-allergic individuals. However, we are not aware of any peer-reviewed published study in which 120 mg of powder per glove (or any other level) has been demonstrated as a safety threshold for either symptom elicitation or sensitization or even for post-surgical granuloma/adhesion development for latex or synthetic non-latex gloves. This labeling comment is completely inappropriate when applied only to synthetic non-latex gloves as proposed of which there is little data to support adverse reaction claims at the proposed level.

Similar to our comments above concerning latex content values, 120 mg of powder per glove represents a much different powder level on a small glove than on a large glove and should be expressed in relation to surface area. Furthermore, the current analytical method for determination of powder on a powdered glove may not be sufficiently rigorous to provide this arbitrary level with much accuracy.

As with the above comments regarding latex content labels, it is not appropriate to mix caution statements with content labels as this often implies to the user that products below the recommended levels are safe for use.

3. **Expiration date labeling (*Proposed 21 CFR 801.440(d)*)**
With regard to surgeon's gloves, it seems inappropriate to require real time or accelerated aging studies to support shelf-life data that is not applicable to the product. As the maintenance of sterility or packaging integrity generally supercedes any expiration date based upon physical and mechanical integrity, it seems unwarranted to make these potentially useless determinations. Furthermore, it is unclear from the proposed language exactly how the expiration date will be timed. Specifically, does expiration begin from the time of production/manufacture, from the time of chlorination, from the time of packaging or (in the case of sterile product) from the time of sterilization?

How does the Agency plan to address the potential fire hazard issue with their recommendation for shrink wrapping exam gloves that may be of particular concern with the increase of chlorinated gloves? Does the Agency plan additional recommendations for shelf life and physical property assessment of chlorinated products?

4. **Quality System Regulation (21 CFR Part 820) Page 2-9**
It is clear that medical grade examination gloves are being used for a wide variety of applications and procedures within healthcare. Does the Agency plan to more clearly define the "intended use" definition to address performance in use (i.e., chemical exposure, concentration, duration of exposure or wear)? (Page 2-10) What is the Agency's role in determining adherence or compliance with quality system requirements post Pre-Market 510(k) acceptance?

5. **Page 3-5 Orthopedic Gloves**
Does the Agency plan to address the need for additional performance in use requirements (i.e.,

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